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Editorial

Future direction of medical genetics

The genetic revolution began in 1953 when Crick and Watson proposed the double-helix structure of DNA. On 26th June 2000, the first draft of the 3.2 billion bases of DNA (the human genome) was made public. The completion of the sequencing of human DNA, undoubtedly the greatest biological achievement will have major implications for the future direction of medical genetics and medicine. The practical value of the completed DNA sequence will be to provide more rapid approaches in the search for disease-causing genes which will lead to the unravelling the molecular basis of disease. It will also provide techniques for accurate and improved diagnosis and for the presymptomatic screening of 'at risk' individuals within families and populations. An understanding of the genetic factors involved in multifactorial conditions, such as ischaemic heart disease and diabetes, will result in the development of personalized prevention, tailored drug treatment and eventually 'cure.'

The clinical geneticist's primary function will continue to be the provision of diagnosis and counselling of families with genetic and partly genetic disorders. They will have the facilities to make accurate diagnoses and to screen family relatives more efficiently for the disease causing gene mutations. It will be possible to make accurate assessment of risk and to provide more detailed information to enable patients and their relatives to make informed decisions. As many clinical disciplines embrace molecular medicine, the clinical geneticist will be a member in multi-discipline teams managing patients with single gene defects and complex disorders Clinicians will have direct access to analysis of gene expression using DNA micro-array technology. This will enable the simultaneous analysis of a thousands of unique DNA fragments, each fragment able to detect mRNA expressed from its corresponding gene. Micro-arrays have huge potential for many different fields in medicine, particularly in gene expression pattern recognition which characterizes disease states.[1] Gene expression profiling will not only be useful for haematological diseases and cancers, but also in unravelling the molecular aetiology of learning disability, skeletal dysplasias and 'dysmorphic' syndromes. Chromosomal analysis (cytogenetics) remains the main diagnostic test for learning disability, genetic syndromes and for reproductive loss and infertility. Currently, chromosomal abnormalities are diagnosed by conventional G- or R-banding methods but new techniques based on DNA hybridisation (FISH), spectral karyotyping (SKY) and spectral colour banding (SCAN) will enhance the ability of clinical cytogenetic laboratories to detect subtle genomic changes.[2] The development of whole genome matrix-comparative genomic hybridisation is likely to achieve a resolution equivalent to that of standard of G-banding. A whole genome micro-array will be ideal for screening for microdeletions and microduplications and will greatly assist in the identification of cryptic telomeric aberrations which have a role in unexplained learning disability and dysmorphic syndromes. It will also be a valuable asset in the study of chromosomal aberrations in cancer and will have a major impact on the understanding of disease, disease progression and outcome and also on responses to drug and radiotherapy treatments.

Clinical geneticists and obstetricians are involved in assessing the health of the human fetus. A major challenge is to develop methods which do not compromise the fetus. Currently, prenatal diagnosis of chromosomal abnormalities such as Down syndrome and gene disorders such as Duchenne muscular dystrophy can only be accurately achieved by chorion villus biopsy and amniocentesis which are associated with a 1-5% fetal loss. In the future, clinicians will be able to screen the fetus for chromosomal abnormalities and gene disorders on maternal blood at 10 weeks gestation. The recent discovery of acellular fetal DNA in plasma from pregnant women offers an alternative to invasive procedures.[3] Many pregnant women who are 'at risk' of having an infant with a single gene disorder or a congenital abnormality are reluctant to undergo prenatal diagnosis because abortion is unacceptable. Another approach for such women will be

preimplantation genetic diagnosis(PGD) which will avoid the birth of affected children.[4] Several embryos are produced by IVF and cultured for 3 days to reach a 6-10 cell stage. One or two cells are removed from each embryo and analysed for the specific genetic disorder. Unaffected embryos are transferred to the mother's uterus and thus the resulting baby must be free of the genetic disorder. Currently, PGD is available only for chromosomal trisomies and a few gene disorders such as cystic fibrosis and Duchenne muscular dystrophy. The goal in medicine is to 'cure' disease. Understanding the molecular basis of genetic disorders offers the possibility of correction of the gene defect. Gene therapy is only 10 years old but despite set-backs and obstacles, evidence now is emerging of beneficial outcomes. Trials of gene therapy for severe combined immune deficiency(SCID) and haemophilia have demonstrated that it is possible to restore and maintain normal gene function. Currently gene therapy involves the delivery of the wild type (normal) gene into the affected cells but within the next decade more efficient approaches will be available such as gene repair, engineered exon skipping and 'in utero' gene therapy.[5]

The advances in human genetics raise many legal, ethical and social issues. Clinical geneticists will become increasingly involved in public debate about the application of genetic knowledge not only to families but also to society. Despite the potential for misuse of genetic knowledge, there are enormous benefits of the 'new genetics' to tomorrow's clinical geneticists and physicians. When questioned about the implications of the sequencing of the human genome, J D Watson replied, "Use it . . . to understand more about disease, prevent genetic diseases coming into existence and possibly finding a way to cure them." Clinical genetics has an promising future.

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